

## CLAIMS

We claim:

1. A targeting construct comprising:
  - (a) a first polynucleotide sequence homologous to an alpha-endosulfine gene;
  - (b) a second polynucleotide sequence homologous to the alpha-endosulfine gene; and
  - (c) a selectable marker.
2. The targeting construct of claim 1, wherein the targeting construct further comprises a screening marker.
3. A method of producing a targeting construct, the method comprising:
  - (a) providing a first polynucleotide sequence homologous to an alpha-endosulfine gene;
  - (b) providing a second polynucleotide sequence homologous to the alpha-endosulfine;
  - (c) providing a selectable marker; and
  - (d) inserting the first sequence, second sequence, and selectable marker into a vector, to produce the targeting construct.
4. A method of producing a targeting construct, the method comprising:
  - (a) providing a polynucleotide comprising a first sequence homologous to a first region of the alpha-endosulfine gene and a second sequence homologous to the alpha-endosulfine gene; and
  - (b) inserting a positive selection marker in between the first and second sequences to form the targeting construct.
5. A cell comprising a disruption in an alpha-endosulfine gene.
6. The cell of claim 5, wherein the cell is a murine cell.
7. The cell of claim 6, wherein the murine cell is an embryonic stem cell.
8. A non-human transgenic animal comprising a disruption in an alpha-endosulfine gene.
9. A cell derived from the non-human transgenic animal of claim 8.
10. A method of producing a transgenic mouse comprising a disruption in the alpha-endosulfine gene, the method comprising:

- (a) introducing the targeting construct of claim 1 into a cell;
- (b) introducing the cell into a blastocyst;
- (c) implanting the resulting blastocyst into a pseudopregnant mouse, and
- (d) identifying the transgenic mouse comprising a disruption in the alpha-endosulfine gene.

11. A method of identifying an agent that modulates the expression or function of alpha-endosulfine, the method comprising:

- (a) providing a non-human transgenic animal comprising a disruption in an alpha-endosulfine gene;
- (b) administering an agent to the non-human transgenic animal; and
- (c) determining whether the expression or function of alpha-endosulfine in the non-human transgenic animal is modulated.

12. A method of identifying an agent that modulates the expression or function of alpha-endosulfine, the method comprising:

- (a) providing a cell comprising a disruption in an alpha-endosulfine gene;
- (b) contacting the cell with an agent; and
- (c) determining whether expression or function of alpha-endosulfine is modulated.

13. An agent identified by the method of claim 11 and claim 12.

14. The non-human transgenic animal of claim 8, wherein the transgenic animal exhibits less body weight than wild-type mice

15. The non-human transgenic animal of claim 8, wherein the transgenic animal exhibits improved glucose tolerance.

16. The non-human transgenic animal of claim 8, wherein the transgenic animal exhibits blood glucose sensitivity to exogenous insulin.

17. The non-human transgenic animal of claim 8, wherein the transgenic animal exhibits impaired glucose secretion while on a high fat diet.

18. The non-human transgenic animal of claim 8, wherein the transgenic animal exhibits hyperactivity.

19. A method of screening for biologically active agents, the method comprising:

(a) combining a putative agent with a mammalian alpha-endosulfine polypeptide; and

(b) detecting an effect of said agent on alpha-endosulfine activity; wherein detection of a decrease or an increase in alpha-endosulfine activity is indicative of a biologically active agent.

20. A method of screening for biologically active agents, the method comprising:

(a) combining a putative agent with an isolated cell comprising a nucleic acid encoding a mammalian alpha-endosulfine gene or a alpha-endosulfine promoter sequence operably linked to a reporter gene; and

(b) detecting an effect of said agent on alpha-endosulfine activity; wherein detection of a decrease or an increase in alpha-endosulfine activity is indicative of a biologically active agent